REMARKS

Status of the application

Prior to entry of the instant response, claims 1-21 and 23-47 were pending in the subject application. The Examiner is advised that claim 22 has been previously canceled in the preliminary amendment filed by Applicants on February 6, 2008. Among the pending claims, claims 1-20 and 40-47 are withdrawn as directed to non-elected inventions, and claims 31 and 35-39 are withdrawn as directed to non-elected species. Claims 21, 23-30 and 32-34 are under examination and stand rejected in the instant office action.

With entry of the instant response, claims 24 and 27-28 have been canceled without prejudice, and claim 1 has been amended. Specifically, claim 21 has been amended to limit the previously recited microbial infection to bacterial infection. The claim has also been amended to specify treating bacterial infection by production of ozone. Support for this amendment is replete in the specification, e.g., at page 2, 2nd paragraph; page 13, last full paragraph; page 20, last paragraph; and page 22, 3rd paragraph. Claim 21 has further been amended to indicate that the sensitizer molecule is not conjugated to the antibody. Support for this amendment is provided in the specification. For example, at pages 73, 78 and 87, the specification discloses bactericidal assays wherein an antibody and a sensitizer molecule of different concentrations (i.e., no conjugation between the two molecules) were added to a bacterial culture (e.g., E. coli or S. typhmurium). Morever, at page 23, 4th paragraph, the specification discloses that some embodiments of the invention employ a sensitizer that is conjugated to the antibody. By implication, the specification inherently discloses other embodiments wherein the sensitizer is not conjugated to the

antibody. As stated in the MPEP, other than express disclosure, claim limitations can also be supported in the specification by implicit or inherent disclosure (See, e.g., MPEP. § 2163-I-B).

Applicant submit that the claim amendments introduced herein do not introduce new matter. Unless otherwise noted, the claim amendments have been made to better present Applicants' inventions and should not be construed as acquiescence of any ground of rejections. The following remarks address the substantive issues raised in the instant Office Action.

Claim Objection

Claim 22 was objected to as allegedly being in improper dependent form. In response, Applicants note that, as pointed out above, claim 22 has been previously canceled in the preliminary amendment encompassed by the response to restriction requirement that was filed by Applicants on February 6, 2008.

Rejection under 35 USC §103

Claims 21-23, 25, 29-30 and 33 were rejected as allegedly being obvious over Harmon et al. (WO 1988/008135) in view of Hasan et al. (USPN 7,268,155). Claims 21-34 were rejected as allegedly obvious over Harmon et al. in view of Hasan et al., Goers et al. (WO 1986/001720); Wentworth et al. (Proc. Natl. Acad. Sci. USA 97:10930-5, 2000); and Devanathan et al. (Proc. Natl. Acad. Sci. USA 87:2980-4, 1990). The Examiner asserts that Harmon et al. teaches method of preventing bacterial infection by administering a monoclonal antibody capable of binding to an epitope on a gram negative bacterial core, that Hasan et al. teaches a method of treating staph infection with a conjugate comprising a polylysine backbone coupled to a targeting moiety and a photosensitizer, that Goers et al. teaches an antibody-

therapeutic agent conjugate, and that Wentworth et al. teaches conversion of molecular oxygen into hydrogen peroxide by antibodies. The Examiner then concludes that the presently claimed invention would have been prima facie obvious over the cited art.

Applicants respectfully disagree with the reasoning underlying each of the noted rejections. However, in an effort to advance prosecution of the subject application, Applicants have amended the pending claims which are now directed to methods wherein the recited sensitizer molecule is not conjugated to the antibody. In addition, the claims are also amended to specify production of ozone in the treatment. As detailed below, the presently claimed invention is undoubtedly nonobvious and patentable over the cited art.

As background information, the present invention is based in part on the surprising discoveries by the present inventors that trioxygen species such as ozone, which were not previously known or expected to present in any in vivo system (e.g., a cell, or a human or animal body), can actually be produced in vivo as a result of antibodies' catalytic activities when singlet oxygen is present. The inventors also found that reactive oxygen species thus produced have bactericidal activities in vivo. Such important discoveries and related work were first reported in scientific literature by the present inventors and co-workers, e.g., Wentworth et al., Science 298:2195-9, 2002 *(Evidence for antibody-catalyzed ozone formation in bacterial killing and inflammation)*; Wentworth et al., Proc Natl Acad Sci U S A. 100:1490-3, 2003 *(Evidence for the production of trioxygen species during antibody-catalyzed chemical modification of antigens)*; and Wentworth et al., Science 302:1053-6, 2003 *(Evidence for ozone formation in human atherosclerotic arteries)*.

As specified in the present claims, the subject invention is directed to applications of the previously unknown activity of antibodies to catalyze the production of ozone for treating bacterial infections in an in vivo system (in "a mammal").

Claims 21-23, 25, 29-30 and 33 were rejected as being obvious over Harmon et al. and Hasan et al. Hamon et al. discusses the use of antibodies to target a specific epitope of a bacterium. The Hasan et al. reference discusses the use of a photosensitizer conjugated to a peptide targeting agent for treating microbial infection (e.g., staph infection). However, these references do not teach or suggest production of ozone in vivo or their bactericidal activity. In rendering the rejection, the only reasoning set forth in the office action is simply that "both teach a method treating a bacterial infection."

Applicants cannot understand the rationale underlying this obviousness rejection. Instead, it would be entirely improper to render an obviousness rejection based on such a conclusory statement. As is well known, in addition to a motivation to combine teachings of the cited art, a prima facie case of obviousness should at least also include a showing of a reasonable expectation of success. In the instant case, Applicants submit that there is neither a motivation to combine the cited art nor a reasonable expectation. First, the fact that two methods are intended for treating the same condition or disease by no means suggest that they can be combined to treat the same condition (let alone the gram negative bacterial infection in Harmon et al. and the gram positive staph infection in Hasan et al., which are surely different conditions). This is because interactions among different drugs or treatment regimens can easily and often lead to severe side effects and/or diminished efficacy. In addition, even assuming one might want

to combine two different treatment regimens for the same disease or conditions, there usually could be no reasonable expectation of success without more information on the drugs involved or until the proposed combination therapy is actually tested (e.g., in laboratory). For example, one would not be motivated to combine Pioglitazone and Glimepiride for diabetic patients merely because both were known to be useful for treating diabetes. One certainly would not have any expectation that such a combination would work without more detailed information on potential drug interactions or opposing effects the two drugs might have on each other. If it is obvious to combine, with reasonable expectation of success, different drugs or treatments just because they are intended for the same disease or condition, then thousands of new combination therapies will be readily available from various treatments currently prescribed for treating a number of human diseases. By common sense, this is certainly not the case. For these reasons, the rejection of the present invention over the combination of Harmon et al. and Hasan et al. is clearly improper and must be withdrawn.

Turning to the rejection of claims 21-34 over Harmon et al. and the other cited references, the Wentforth et al. reference discusses antibody catalyzed production of reactive oxygen species such as hydrogen peroxide. This reference does not teach or suggest antibody-catalyzed production of ozone or in vivo bactericidal activity associated therewith. The other references cited in rendering the instant rejection (i.e., Goers et al. and Devanthan et al.) relate to the use of an antibody as a targeting agent to which is conjugated a therapeutic agent. There is no teaching or suggestion in these references of using an antibody as a catalytic agent to catalyze production of ozone, let alone using a sensitizer molecule that is not conjugated to an

antibody.

Thus, in addition to the improper combination of Harmon et al. and Hasan et al., a prima facie case of obviousness also cannot be established based on Harmon et al. and the additional cited references. This is because prior to the subject invention, it is simply not known or expected in the art that ozone can be produced in vivo by antibody catalyzed reactions or otherwise. As a result, unlike the present invention which exploits bactericidal activity of in vivo generated ozone, the therapeutic methods discussed in the cited art (other than the Wentworth et al. paper) all employ an antibody as the therapeutic agent itself or as a targeting agent for delivering a different therapeutic agent (e.g., a photolytic agent or photosensitizer). Because the antibody was employed as a targeting agent, the photolytic agent or photosensitizer used as the therapeutic agent in the cited art (e.g., Goers et al. and Devanathan et al.) all need to be conjugated to the antibody. Due to the fundamentally different mechanisms between the methods disclosed in the cited art and the present invention, it would be entirely unreasonable to conclude that the claimed invention would have been obvious over the cited art.

Also, none of the additional references teaches the use of a sensitizer molecule that is not conjugated to an antibody or targeting agent. Therefore, even assuming for the sake of argument that one would be motivated to combine the cited references, a prima facie case of obviousness nonetheless cannot be established because the combined teachings do not disclose each and every element of the presently claimed invention. Applicants accordingly respectfully request that the instant rejections be withdrawn.

Rejection under 35 USC §112, 1st paragraph, enablement

Claims 21-30 and 32-34 were rejected as allegedly not enabled. It is alleged in the office action that the specification, while enabling methods of treating Salmonella infection, does not enable the methods as claimed. It was also asserted in the office action that the specification does not enable "an antimicrobial composition comprising a sensitizer not attached to an antibody." Applicants respectfully traverse the rejection for the reasons stated below.

The Examiner is advised that therapeutic activities of ozone in treating microbial infection have been known for many years. For example, ozone was shown to be able to inhibit growth and/or inactivate various viruses and bacteria. Bacteria that were killed by ozone treatment include both gram negative and gram positive bacteria such as Escherichia coli, Salmonella sp., Staphylococcus aureus and Bacillus subtilis. See, e.g., Thanomsub et al., J Gen Appl Microbiol. 48:193-9, 2002 (*Effects of ozone treatment on cell growth and ultrastructural changes in bacteria*); and Burleson et al., Appl. Microbiol. 29:340-4, 1975 (*Inactivation of viruses and bacteria by ozone, with and without sonication*). Thus, the prior art has clearly taught how to use ozone in therapeutic applications for treating microbial infections.

On the other hand, the present invention is not based on identification of any novel therapeutic effects (e.g., microbial killing) of ozone or other reactive oxygen species disclosed in the specification. Rather, the invention resides in part on the discovery by the present inventors that ozone, which is not previously known to be present in any in vivo system, can actually be produced in vivo as a result of antibodies' catalytic activities when singlet oxygen is present. Such important

discoveries were also reported in several post-filing publications by the present inventors and co-workers, e.g., Wentworth et al., Science 298:2195-9, 2002 *(Evidence for antibody-catalyzed ozone formation in bacterial killing and inflammation)*; Wentworth et al., Proc Natl Acad Sci U S A. 100:1490-3, 2003 *(Evidence for the production of trioxygen species during antibody-catalyzed chemical modification of antigens)*; and Wentworth et al., Science 302:1053-6, 2003 *(Evidence for ozone formation in human atherosclerotic arteries)*.

Thus, the presently claimed invention is predicated on known therapeutic activities of ozone in an in vivo system where presence of ozone was not previously known or expected. As discussed above, therapeutic methods of using ozone to treat microbial infection per se are enabled because of teachings in the prior art. In addition to the prior art teachings, the subject specification has exemplified methods of using in vivo produced ozone to kill bacteria such as E. coli (e.g., at page 78 and Figures 14-17) and S. typhmurium (e.g., at page 87 and Figure 21). It is worth noting that, contrary to the Examiner's assertion, the antibodies are not conjugated or attached to the sensitizer molecule (e.g., hematoporphin IX) in these specific examples.

Moreover, in an effort to advance prosecution of the subject patent application, Applicants have amended independent claim 21 which now recites only bacterial infection. Therefore, it is readily apparent that the claimed methods are enabled by the subject disclosure and knowledge well known in the art. In light of the clarifications and claim amendment presented herein, Applicants respectfully urge that the instant rejection should be withdrawn.

Rejection under 35 USC §112, 1st paragraph, written description

Claims 21-34 were rejected as alleged not complying with the written description requirement. The rejection appears to be based on the Examiner's belief that description of the subject specification is limited to treating bacterial infection, not any other microbes encompassed by the present claims.

Applicants do not agree with the rationale underlying the instant rejection. However, as indicated above, Applicants have further amended the claims which are now directed to treating only bacterial infections. As disclosed in the specification and also acknowledged by the Examiner, the subject specification has provided extensive description of how to generate reactive oxygen species such as ozone in vivo to kill or inhibit the growth of bacteria, including how to providing antibody activity, sources of singlet oxygen, and various bacterial species suitable for the therapeutic methods (See, e.g., pages 20-25). Methods of evaluating anti-microbial activity and effective dosages are also disclosed in the specification (see, e.g., page 26). Further, the specification provides more detailed guidance and specific procedures for practicing the present invention with exemplified bacterial species such as Escherichia and Salmonella (see, e.g., Examples III and IV).

Furthermore, as explained above, therapeutic activities of reactive oxygen species such as ozone in microbial infection are well known in the art. As is well established in the law, a patent specification "need not teach, and preferably omits, what is well known in the art." See *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534, 3 USPQ2d 1737, 1743 (Fed. Cir. 1987); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). For all these reasons, a skilled artisan would readily conclude that the subject

specification, in combination with knowledge well known in the art, has provided adequate description of the presently claimed invention. Accordingly, the instant rejection should be withdrawn.

Rejections under 35 USC 112, 2nd paragraph

Claims 27-28 were rejected as allegedly being indefinite. Specifically, it was noted in the office action that there is insufficient antecedent basis for the recitation of "reactive oxygen species" in the claims.

To facilitate prosecution of the subject patent application, Applicants have also canceled claims 27 and 28 herein. The instant rejections are therefore moot.

CONCLUSION

In view of the foregoing, Applicants respectfully submit that the claims now pending in the subject patent application are in condition for allowance, and notification to that effect is earnestly requested. If a telephone conference would expedite prosecution of this application, please telephone the undersigned attorney at 858-784-2937.

The Director is hereby authorized to charge our Deposit Account No. 19-0962 in the event that there are any additional charges associated with the present Petition or any Response in connection with this application.

Respectfully submitted,

July 18, 2008
Date

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